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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/600,714	10/04/00	FLEGEL W	12086-002001

HM12/0925

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EXAMINER	
HUYNH, P	
ART UNIT	**PAPER NUMBER**
1644	12

DATE MAILED: 09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/600,714	FLEGEL ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/5/01; 7/9/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *13 and 15-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-48 are pending.

2. Applicant's election of Group I, claims 1-12, 14 and 48, filed 7/9/01, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 13, 15-47 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-12, 14 and 48 are acted upon in this Office Action.

5. Preliminary Amendment to Figures 2 and 3, filed 1/5/01, has not been entered. Applicant is reminded that the Patent and Trademark Office no longer makes drawing changes and that it is applicant's responsibility to ensure that the formal drawings for Figures 2 and 3 on pages 3/5 and 4/5 have SEQ ID NOS.

It is suggested that applicant amend the Brief Description of the Drawings to include SEQ ID NOS. See 37 CFR 1.821(d).

6. Applicant should amend the first line of the specification to reflect the relationship between the instant application and PCT EP 98/08319, filed 12/18/98.

7. The drawings, filed 10/4/00, are not approved.

8. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

9. The disclosure is objected to because of the following informalities: (1) Typographical errors "high grade D"" on page 2 line 2; (2) "(D-test ")" on page 28 line 15; "2" on the last line of page 33 should be subscript. Appropriate correction is required.

10. Claims 8, 11-12 and 48 are objected to because of the following informalities:
(1) There are numerous typographical errors "II", "AIIT", "CIIG" throughout claim 8; it is suggested that Applicant amend the claim to recite "from T to A" at position 544, for example.
(2) The word "cell" is missing in claim 11 and claim 12, line 2.
(3) Claim 48 recites non-elected invention. Appropriate correction is required.

11. Claim 5-12, 14 and 48 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-12, 14 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) polynucleotide of SEQ ID NO: 41 and (2) oligonucleotides represented by SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 for screening missense mutation in *RHD* gene, does not reasonably provide enablement for (1) *any* nucleic acid molecule encoding a Rhesus D antigen contributing to or indicative of the weak D phenotype wherein said nucleic acid molecule carrying at least one missense mutation as compared to the wild type Rhesus D antigen in its transmembrane and/or intracellular regions (2) *any* nucleic acid molecule carrying at least one missense mutation as compared to the wild type Rhesus D antigen in amino acid positions 2-16, 114-149, 179-225 or/and 267 to 397 with the proviso that said D antigen does carry not a single missense mutation leading to a substitution of phenyalaline in amino acid position 223 by valine or of threonine in position 283 by isoleucine or carrying a gene conversion involving exons 6 to 9 which are replaced the corresponding exons of the *RHCE* gene, (3) *any* nucleic acid molecule carrying missense mutation that causes an amino acid substitution in position 3, 10, 16, 114, 149, 182, 198, 201, 220, 223, 270, 276, 277, 282, 294, 295, 307, 339, 385 or 393 or a combination thereof involving said substitutions, (4) any nucleic acid molecule of claim 3 carrying missense mutation that causes an amino acid substitution in various position as recited in claim 4, (5) any nucleic molecule of any one of claims 1 to 4 carrying missense mutation occurs in various nucleotide positions as recited in claim 5, (6) *any* nucleic acid molecule of claim 5 carrying missense mutation occurs in various nucleotide positions as recited in claim 6, (7) *any* nucleic acid molecule of claim 3 or 4 carrying a combination of substitution in various nucleotide positions as recited in claim 7, (8) *any* nucleic acid molecule of claim 5 or 6 carrying a combination of missense mutations as recited in claim 8, (9) *any* nucleic acid molecule of any one of claims 1 to 8 which is mRNA or genomic DNA, (10) any vector comprising said nucleic acid molecule mentioned above, (11) any non-human host cell transformed with said vector, (12) any method of producing a Rhesus D comprising culturing said host cell, (13) *any* oligonucleotides hybridizing under "stringent conditions" to a portion of any nucleic acid molecule of any one of claims 1 to 9 comprising at least one missense mutation, (14) *any* complementary portion thereof, (15) *any* region involving the breakpoint of the gene conversion and (16) any kit comprising said nucleic acid molecule mentioned above for screening blood of donor and recipient for the presence of one or more missense mutation in the Rh D antigen. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes a Rhesus D antigen carrying one or more missense mutations which contribute to weak D phenotype and (2) oligonucleotides of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 shown in Table 1 on page 33 that are *RHD* specific for screening missense mutation in *RHD* gene.

With the exception of SEQ ID NO: 41, the specification does not teach how to make and use *any* "nucleic acid molecules" mentioned above that would encode a Rhesus D antigen which contribute to a weak D phenotype as a consequence of missense mutation because the structure and function associated with said nucleic acid molecules are not disclosed. By reciting "nucleic acid molecule" in the preamble of the instant claims 1-9, the said "nucleic acid molecule" can encompass an infinite number of polynucleotide that may or may not encode a Rhesus D antigen. Given the indefinite number of "nucleic acid molecule" and there is no guidance in the specification as to which position within the full length of said "nucleic acid molecule" that after substitution, deletion or insertion will retain both structure and function similar to SEQ ID NO: 41 or contribute to weak D phenotype, it is unpredictable to determine which undisclosed "nucleic acid molecule" would be useful for screening the presence of one or more missense mutation in Rh D antigens of blood of donor and recipient. Since the specification fails to provide guidance regarding which nucleotide within said "nucleic acid molecule" can tolerate change, it follows that the amino acid encoding by said "nucleic acid molecule" is not enable. Because of the indefinite number of "nucleic acid molecule" encompassed by the claims, the vector comprising any undisclosed "nucleic acid molecule" of any one of claims 1 to 9 as recited in claim 10 is not enabled. Since the vector comprising said "nucleic acid molecule" is not

enabled, any non-human host cells to be transformed with said vector and the method of producing a Rhesus D antigen that contributes to the weak D phenotype as recited in claims 11-12 are not enabled.

With regard to oligonucleotide "hybridizing under stringent conditions" as recited in claim 14, the claim encompasses any random sequence of any length which hybridizes under unknown conditions to any undisclosed "nucleic acid molecule" which may or may not encode a Rhesus D antigen carrying missense mutation that contribute to the weak D phenotype. Given the indefinite numbers of oligonucletoides, the lack of guidance and insufficient number of working examples, it is unpredictable to determine which oligonucleotides would hybridize specifically to "nucleic acid molecule" that encodes a Rhesus D antigen and be useful for screening the presence of one or more missense mutation in Rh D antigens of blood of donor and recipient.

The state of the prior art as exemplified by Wallace *et al* and Sambrook *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a Rhesus D antigen. Since the undisclosed oligonucleotide would not hybridize specifically to the "nucleic acid molecule" that encodes a Rhesus D antigen, it follows that the oligonucleotide would not specifically hybridize to the "complementary portion thereof" or any region involving the breakpoint of the gene conversion as recited in claim 14. It follows that any kit comprising said "oligonucletoide" is not enable.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

14. Claims 1-12, 14 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* nucleic acid molecule encoding a Rhesus D antigen contributing to or indicative of the weak D phenotype wherein said nucleic acid molecule carrying at least one missense mutation as compared to the

wild type Rhesus D antigen in its transmembrane and/or intracellular regions (2) *any* nucleic acid molecule carrying at least one missense mutation as compared to the wild type Rhesus D antigen in amino acid positions 2-16, 114-149, 179-225 or/and 267 to 397 with the proviso that said D antigen does carry not a single missense mutation leading to a substitution of phenyalaline in amino acid position 223 by valine or of threonine in position 283 by isoleucine or carrying a gene conversion involving exons 6 to 9 which are replaced the corresponding exons of the *RHCE* gene, (3) *any* nucleic acid molecule carrying missense mutation that causes an amino acid substitution in position 3, 10, 16, 114, 149, 182, 198, 201, 220, 223, 270, 276, 277, 282, 294, 295, 307, 339, 385 or 393 or a combination thereof involving said substitutions, (4) any nucleic acid molecule of claim 3 carrying missense mutation that causes an amino acid substitution in various position as recited in claim 4, (5) any nucleic molecule of any one of claims 1 to 4 carrying missense mutation occurs in various nucleotide positions as recited in claim 5, (6) *any* nucleic acid molecule of claim 5 carrying missense mutation occurs in various nucleotide positions as recited in claim 6, (7) *any* nucleic acid molecule of claim 3 or 4 carrying a combination of substitution in various nucleotide positions as recited in claim 7, (8) *any* nucleic acid molecule of claim 5 or 6 carrying a combination of missense mutations as recited in claim 8, (9) *any* nucleic acid molecule of any one of claims 1 to 8 which is mRNA or genomic DNA, (10) any vector comprising said nucleic acid molecule mentioned above, (11) any non-human host cell transformed with said vector, (12) any method of producing a Rhesus D comprising culturing said host cell, (13) *any* oligonucleotides hybridizing under "stringent conditions" to a portion of any nucleic acid molecule of any one of claims 1 to 9 comprising at least one missense mutation, (14) *any* complementary portion thereof, (15) *any* region involving the breakpoint of the gene conversion and (16) any kit comprising said nucleic acid molecule mentioned above for screening blood of donor and recipient for the presence of one or more missense mutation in the Rh D antigen.

With the exception of SEQ ID NO: 41, there is no description about the structure associated with function of any "nucleic acid molecule" mentioned above, that is critical for screening blood of donor and recipient for the presence of one or more missense mutation in the Rh D antigen. Given that the "nucleic acid molecule" is not adequately described, the complementary thereof and any region involving the breakpoint of the gene conversion are not adequately described for the same reasons as mentioned above. It is noted that though the claimed invention is directed to "nucleic acid molecule", the principle still holds for the amino

acid encoded by said "nucleic acid molecule". Sine only one polynucleotide of SEQ ID NO: 41 that encodes a Rhesus D antigen is disclosed, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

With the exception of oligonucleotides of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40, there is no description about the structure of any "oligonucleotide" because by reciting hybridizing terminology in the claim, the oligonucleotide can encompass an infinite number of oligonucleotide that are capable of hybridizing under any conditions, including low stringency, to any undisclosed "nucleic acid molecule". Given the indefinite number of oligonucleotide that may encompassed by the claim, the oligonucleotide comprising a nucleotide sequence which hybridizes to any nucleic acid molecule "under stringent conditions" is not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

16. Claims 1-12, 14 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "a combination of/or" in claim 3 is ambiguous and indefinite because the meaning "of/or" is not clear.

The recitation of "S182T, K198N, T201R, F223V, W16C, T201R and F223V" in claim 7 is ambiguous. It is suggested that Applicants amend the claim to recite "in position 182 from S to T", for example.

It is indefinite to recite **"preferably"** in Claim 7, lines 2 and 3.

The recitation of "TIIA" in claim 8 is ambiguous. It is suggested that Applicants amend the claim to recite "from T to A", for example.

It is indefinite to recite **"preferably"** in Claim 8, lines 2, 4 and 6.

The recitation of "a non-human host" in claim 11 is ambiguous. It is suggested that "A non-human host cell" be recited in claim 11.

Claim 9 should recite "**wherein** said nucleic acid molecule is mRNA or genomic DNA", **rather than "which is mRNA or genomic DNA".**

The "or" recited in claim 5 has no antecedent basis in base claim 4. Claim 4 recites "and" which requires all amino acid substitution be in included in the claim while claim 5 recites "or" which requires one missense mutation or a combination of missense mutation be included in the claim.

The recitation of "culturing the host" in claim 12 is ambiguous. It is suggested that "culturing the host cell" be recited in claim 12.

The recitation of hybridizing "**under stringent conditions**" in claim 14 is indefinite. These conditions are not defined by the claims and one of ordinary skill in the art would not be reasonably appraised of the metes and bounds of the invention. It is suggested that the specific conditions disclosed on page 34 be recited in the claim. Appropriate correction is required.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 2, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by LeVan *et al* (Blood 83: 3098-3100, 1994; PTO 892).

LeVan *et al* teach a polynucleotide (Accession number A46368) that encodes a Rhesus D antigen carrying one missense mutation at the amino acid position 218 which is within the amino acid position from 114 to 149 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). Claim 9 is include in this rejection because the reference polynucleotide is genomic DNA. LeVan et al further teach PCR primers which are oligonucleotides that hybridize under stringent conditions to a portion of the reference polynucleotide carrying missense mutation or the complementary thereof (See page 3098, in particular). Thus, the reference teachings anticipate the claimed invention.

19. Claims 1-3, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Salvignol *et al* (Biochem Genet 32: 201-221, 1994; PTO 892).

Salvignol *et al* teach a polynucleotide (Accession number I37076) that encodes a Rhesus D antigen carrying one missense mutation at the amino acid position 282 which is within the amino acid position 267 to 397 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). The nucleic acid molecule has a missense mutation that causes an amino acid substitution at position 282 (See enclosed sequence alignment, in particular). Claim 9 is include in this rejection because the reference polynucleotide is genomic DNA. Salvignol *et al* further teach oligonucleotides that hybridize to the reference polynucleotide comprising missense mutation or the complementary or a portion thereof (See Materials and Methods, in particular). Thus, the reference teachings anticipate the claimed invention.

20. Claims 1-5, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Salvignol *et al* (Biochem Genet 32: 201-221, 1994; PTO 892).

Salvignol *et al* teach a polynucleotide (Accession number I37075) that encodes a Rhesus D antigen carrying at least one missense mutation (See enclosed sequence alignment, in particular). The reference polynucleotide carries a missense mutation at the amino acid position range from 2-16, 114-149, 179-225 and 267-397 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). The missense mutation in the reference polynucleotide causes by an amino acid substitution at position at 201 and 270 as recited in instant claim 3 (See enclosed sequence alignment, in particular). The missense mutation in the reference polynucleotide causes by an amino acid substitution at position 16 to Cys as recited in instant claim 4 (See enclosed sequence alignment, in particular). The polynucleotide (nucleic acid molecule) has a missense mutation occurs in nucleotide position 48 as recited in claim 5 (See enclosed sequence alignment, in particular). Claim 9 is include in this rejection because the reference polynucleotide is genomic DNA. Salvignol *et al* further teach primers or oligonucleotides that hybridize under stringent conditions to the reference polynucleotide carrying missense mutation or the complementary thereof (See

Materials and Methods, in particular). Thus, the reference teachings anticipate the claimed invention.

21. Claims 1-4, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Cherif-Zahar *et al* (Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892).

Cherif-Zahar *et al* teach a polynucleotide (Accession number A30405) that encodes a Rhesus D antigen carrying at least one missense mutation (See enclosed sequence alignment, in particular). The reference polynucleotide carries a missense mutation at the amino acid position range from 179-225 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). The missense mutation in the reference polynucleotide causes by an amino acid substitution at position at 182, 198 and 223 as recited in instant claim 3 (See enclosed sequence alignment, in particular).

The missense mutation in the reference polynucleotide causes by an amino acid substitution at position 182 to Thr, at position 198 to Asn, at position Val as recited in instant claim 4 (See enclosed sequence alignment, in particular). Claim 9 is include in this rejection because the reference polynucleotide is genomic DNA (See page 6243, Materials and Methods, in particular). Cherif-Zahar *et al* further teach oligonucleotides (primers) that hybridize to the reference polynucleotide or a portion thereof and the complementary thereof carrying missense mutation (See page 6243, Materials and Methods, in particular). Thus, the reference teachings anticipate the claimed invention.

22. Claims 1-3, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Salvignol *et al* (Biochem Genet 32: 201-221, 1994; PTO 892).

Salvignol *et al* teach a polynucleotide (Accession number I84434) that encodes a Rhesus D antigen carrying at least one missense mutation (See enclosed sequence alignment, in particular). The reference polynucleotide carries a missense mutation at the amino acid position range from 114-149 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). The missense mutation in the reference polynucleotide causes by an amino acid substitution at position at 149, 198 and 223 as recited in instant claim 3 (See enclosed sequence alignment, in particular). Claim

9 is include in this rejection because it is genomic DNA. Salvignol *et al* further teach oligonucleotides (primers) that hybridize to the reference polynucleotide comprising missense mutation or the complementary or a portion of thereof (See Materials and Methods, in particular). Thus, the reference teachings anticipate the claimed invention.

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 10-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over LeVan *et al* (Blood 83: 3098-3100, 1994; PTO 892), Salvignol *et al* (Biochem Genet 32: 201-221, 1994; PTO 892) or Cherif-Zahar *et al* (Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892) each in view of Sambrook *et al* (*Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17).

The teachings of LeVan *et al*, Salvignol *et al* and Cherif-Zahar *et al* have been discussed supra.

The claimed invention in claim 10 differs from the references only by the recitation of a vector comprising the nucleic acid encoding Rhesus D antigen.

The claimed invention in claim 11 differs from the references only by the recitation of a non-human host cell transformed with the vector of claim 10.

The claimed invention in claim 12 differs from the references only by the recitation of a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing a host cell of claim 11 under suitable conditions and isolating the Rhesus D antigen.

The claimed invention in claim 14 differs from the references only by the recitation of an oligonucleotide hybridizing under stringent conditions to a portion of the nucleic acid molecule of any one of claims 1 to 9 comprising said at least one missense mutation or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2.

Sambrook *et al* teach cloning a cDNA into an expression vector, a process of transforming the expression vector into host cells, culturing the host cells under conditions in which the polypeptide is expressed and then recovering the polypeptide from the culture. Sambrook *et al* teach that it is desirable to use recombinant DNA techniques for the production of biologically active proteins in order to produce proteins of higher concentration and purity. Sambrook *et al* further teaches how to make and use oligonucleotide probes that hybridize to any polynucleotide and guidelines for selection of conditions that promote maximal specificity of hybridization for screening and rapid isolation of cloned copies of genes (See chapter 11, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce the Rhesus D antigen by constructing an expression vector with the polynucleotide which encodes the Rhesus D antigen as taught by of LeVan *et al*, Salvignol *et al* or Cherif-Zahar *et al* and producing a recombinant host cell using the said expression vector and culturing the host cell under conditions which express the polypeptide in order to recover the polypeptide from the culture as taught by the Sambrook *et al*. It would be been obvious to one having ordinary skill in the art at the time the invention was made to produce oligonucleotide as taught by Sambrook *et al* that would hybridize to the nucleic acid molecule encoding a Rhesus D antigen as taught by LeVan *et al* or Salvignol *et al* or Cherif-Zahar *et al*.

One having ordinary skill in the art at the time the invention was made would have been motivated to produce said polypeptides using recombinant techniques because there would be a higher yield of polypeptide with greater purity as taught by Sambrook *et al*. Sambrook *et al* teach the use oligonucleotides for screening and rapid isolation of cloned copies of large numbers of genes.

26. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over LeVan *et al* (Blood 83: 3098-3100, 1994; PTO 892), Salvignol *et al* (Biochem Genet 32: 201-221, 1994; PTO 892) or Cherif-Zahar *et al* (Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892) each in view of Sambrook *et al* (*Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17) as applied to claims 10-12 and 14 and further in view of US Pat No. 6,200,802 (Filed Oct 1993, PTO 892).

The teachings of LeVan *et al*, Salvignol *et al*, Cherif-Zahar *et al* and Sambrook *et al* have been discussed supra.

The claimed invention in claim 48 differs from the references only by the recitation of a kit comprising the oligonucleotide.

The '802 patent teaches a kit comprising oligonucleotide for screening assays (see column 33, lines 43-50, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to oligonucleotide as taught by the '820 patent with the oligonucleotide as taught by Sambrook *et al* that hybridizes to the polynucleotide as taught by LeVan *et al*, Salvignol *et al* or Cherif-Zahar *et al* and packing it in a kit for various screening assays as taught by the '802 patent with the expectation that a kit will allow for convenience and commercial expedience. From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

27. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over LeVan *et al* (Blood 83: 3098-3100, 1994; PTO 892) or Salvignol *et al* (Biochem Genet 32: 201-221, 1994; PTO 892) or Cherif-Zahar *et al* (Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892) each in view of US Pat No. 6,200,802 (Filed Oct 1993, PTO 892).

The teachings of LeVan *et al* (Accession number A46368), Salvignol *et al* (Accession number I37076; Accession No. I37075; Accession No. I84434) and Cherif-Zahar *et al* (Accession No. A30405) have been discussed supra.

The claimed invention in claim 48 differs from the references only by the recitation of a kit comprising the oligonucleotide.

The '802 patent teaches a kit comprising oligonucleotide for screening assays (see column 33, lines 43-50, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to put the oligonucleotides as taught by LeVan *et al* or Salvignol *et al* or Cherif-Zahar *et al* in a kit as taught by the '802 patent with the expectation that a kit will allow for convenience and commercial expedience. From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

28. No claim is allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

30. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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September 24, 2001

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